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Original Article

A 2-week efficacy and safety study of gaboxadol and zolpidem using electronic diaries in primary insomnia outpatients

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ABSTRACT

Objectives: To evaluate the efficacy and safety profile of gaboxadol, a selective extrasynaptic GABA$_{\text{A}}$ agonist (SEGA) previously in development for the treatment of insomnia.
Methods: This was a randomised, double-blind, placebo-controlled, parallel-group, 2-week, Phase III study of gaboxadol 5, 10 and 15 mg in outpatients meeting the DSM-IV criteria of primary insomnia ($N = 742$). Zolpidem 10 mg was used as active reference.
Results: At weeks 1 and 2, significant improvement in total sleep time (sTST) compared to placebo was seen for all doses of gaboxadol (all $p < 0.05$). In addition, gaboxadol 10 and 15 mg decreased the number of awakenings (sNAW) ($p < 0.05$) while only gaboxadol 15 mg improved wakefulness after sleep onset (sWASO) ($p < 0.05$). At week 1, all doses of gaboxadol significantly improved time-to-sleep onset (sTSO) ($p < 0.05$). At week 2, a sustained effect on sTSO was observed for gaboxadol 15 mg. Zolpidem also showed effect on all of these variables. Gaboxadol and zolpidem improved sleep quality, freshness after sleep, daytime function and energy at both weeks. Transient rebound insomnia was observed following discontinuation of treatment with zolpidem, but not gaboxadol.
Conclusions: Gaboxadol 15 mg treatment for 2 weeks significantly improved sleep onset and maintenance variables as well as sleep quality and daytime function, as did zolpidem. Gaboxadol 5 and 10 mg also showed benefits on most efficacy variables. Gaboxadol was generally safe and well tolerated, with no evidence of withdrawal symptoms or rebound insomnia after discontinuation of short-term treatment. For zolpidem, transient rebound insomnia was observed.

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1. Introduction

Insomnia is a prevalent complaint and is estimated to affect up to one-third of the adult population [1] and may have adverse consequences for the individual and society [2].

Most of the commonly prescribed hypnotics are categorised as benzodiazepine receptor agonists (BzRAs) which modulate the γ-aminobutyric acid (GABA) subtype A receptor – the key mediator of fast inhibitory transmission in the central nervous system [3].

The presence of an α_4, α_6 or δ subunit in the GABA$_{\text{A}}$ receptor complex confers insensitivity towards benzodiazepines [4]. These benzodiazepine-insensitive receptor subtypes are predominantly located outside the synaptic cleft [5,6] (also termed extrasynaptic receptors) where they mediate the tonic inhibitory currents thought to play a key role in the refinement of the neuronal firing pattern [7,8]. Gaboxadol is a novel selective extrasynaptic GABA$_{\text{A}}$ agonist (SEGA); the $\alpha_4\delta$ containing receptor subtype currently seems the most relevant target mediating its hypnotic activity [9].

The aim of the present study was to confirm the acute hypnotic effects of gaboxadol (observed in previous studies in healthy subjects in a model of transient insomnia [10,11] and in primary insomnia patients [12,13]) in patients with primary insomnia, following a longer treatment duration as required by European guidelines [14]. The study included zolpidem (10 mg) as a reference. Zolpidem was previously proven efficacious on sleep onset and maintenance [15,16].

On March 28, 2007 Lundbeck and Merck announced the discontinuation of the development program for gaboxadol in the treatment of insomnia, based on an assessment of the overall clinical profile of the compound.

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2. Methods

2.1. Design

This was a randomised, double-blind, 5-arm study to compare the effects of gaboxadol 5 mg, 10 mg, and 15 mg versus placebo on subjective sleep variables over 2 weeks, and in a randomised run-out over 1 week. Zolpidem 10 mg was included as an active reference. The design also allowed evaluation of impact of the hypnotic treatments on patient-rated sleep quality and overall daytime performance. The study was conducted at 73 centres in Europe and Canada. Patients were enrolled between 29 January 2003 and 1 September 2004.

2.2. Patients

Outpatients aged 18–65 years who met DSM-IV criteria [17] for primary insomnia were enrolled. Patients also had to have a usual bedtime between 20:00 and 24:00 h and had to meet the following criteria: self-reported total sleep time (sTST) <6 h and self-reported time-to-sleep onset (sTSO) $\geqslant$45 min on at least 4 out of 7 nights. These criteria had to be fulfilled the month prior to screening (a retrospective clinical evaluation) and again during the 1-week, single-blind, run-in phase (prospective daily recording of sleep data using an electronic sleep diary). Patients with a history or current abuse or dependence on any substance with abuse potential, any psychotic disorder, or any other current Axis I diagnosis other than primary insomnia were excluded. The following medications were prohibited prior to the screening visit: within 1 week – any psychoactive or hypnotic drug (including herbal remedies), benzodiazepines, any opiate or opiate derivative containing drug, itraconazol or rifampicin; within 2 weeks – sedating antihistamines, antiepileptics, flurazepam, or diazepam; within 5 weeks – fluoxetine. Patients were excluded if they (a) consumed more than 14 units (women) or 21 units (men) of alcohol a week, or (b) consumed more than 5 caffeine-containing beverages a day, or (c) consumed more than the nicotine-equivalent of 15 cigarettes a day.

All patients gave written informed consent after full explanation of the study procedures and prior to any study-related activity. The study was approved by the appropriate ethics committee for each participating centre and was performed in accordance with good clinical practice (GCP) and the Declaration of Helsinki.

2.3. Procedure

Patients attended a screening visit during which their demographic data, medical, psychiatric, and medication history, and symptoms of insomnia were recorded based on a structured interview and a physical examination. The psychiatric examination was performed using the Mini International Neuropsychiatric Interview (MINI) [18] to rule out comorbidities. Only investigators were trained and allowed to perform the MINI and structured interview. Eligible patients underwent a 1-week, single-blind, placebo run-in phase (baseline week). For data collected on a daily basis (patient diaries), the mean scores during the run-in phase served as baseline. For data collected at the patient visits (LSEQ), the randomisation visit at the end of the run-in week served as baseline. Patients who continued to meet the eligibility criteria at the end of the run-in week were randomised to 2 weeks of treatment with one of the following: gaboxadol 5 mg, gaboxadol 10 mg, gaboxadol 15 mg, zolpidem 10 mg, or placebo. The treatment was followed by a 1-week, double-blind, run-out phase in which 50% of patients previously assigned to an active treatment were randomised to placebo, while the other 50% remained on their existing treatment. There was a 1-week safety follow-up period after the end of the run-out phase.

The randomisation code was generated by a statistician at H. Lundbeck A/S. Patients were randomised in a 1:1:1:1:1 ratio, using a block size of 10. The randomisation code specified the treatment to be received for both the 2-week treatment phase and the 1-week run-out phase. The treatments were encapsulated to ensure study blinding. Patients were instructed to take one capsule before bedtime every night throughout the study.

2.4. Efficacy assessments

The patients were each given a hand-held computer electronic diary, programmed with a morning and an evening questionnaire. In the morning questionnaire, a number of variables with respect to the previous evening/night were recorded including sTST, self-reported number of nocturnal awakenings (sNAW), self-reported duration of nocturnal awakenings (i.e., wakefulness after sleep onset, sWASO), sTSO, self-reported quality of sleep (sQUAL), and self-reported freshness after sleep (sFRESH). sQUAL and sFRESH were recorded using a 100-point visual analogue scale (VAS), where 0 points referred to the worst conceivable condition and 100 points referred to the best conceivable condition. Most questions were adapted from a morning patient-self-rating scale [19]. The morning questionnaire was completed after the patient had finished the normal morning waking and bathroom routines. In the evening questionnaire, the following daytime performance variables were recorded with similar 100-point VASs: energy (ENERGY) and ability to function (FUNCTION). For some of the above variables, the VAS was reversed to avoid habitual responses from the patients. The evening questionnaire was completed after dinner and before taking study medication and bedtime.

Patients also assessed their sleep at the end of each week using the Leeds Sleep Evaluation Questionnaire (LSEQ) [20]. This questionnaire consists of ten 100-mm VASs pertaining to four aspects of sleep: (1) getting to sleep, (2) quality of sleep, (3) awakening from sleep, (4) behaviour following wakefulness.

The evaluation of the rebound insomnia was based on sTST and sTSO data from the patient diary in the 1-week randomised run-out phase.

2.5. Safety assessments

Adverse events were recorded throughout the study and were rated by the investigator with regard to intensity and likelihood of being drug-related. Vital signs, ECGs, routine laboratory assessments, and physical examinations were performed at regular intervals.

A Withdrawal Symptoms Questionnaire designed for the use of benzodiazepines [21] was included in the evening diary during the run-out phase.

2.6. Data analysis

All efficacy analyses were based on observed cases (OC) for the population of randomised patients who took at least one dose of double-blind treatment and who had at least one post-baseline assessment of an efficacy variable (full analysis set). The primary measures for the analysis were changes from baseline in the weekly means of sTST, sTSO, sNAW, and sQUAL. sTSO was analysed after transformation with the natural logarithm (log_sTSO) to normalise the distribution. Treatment groups were compared using estimates from a repeated measurements model with an unstructured covariance matrix that included week, centre, and treatment as factors and the baseline value of the variable as a covariate.

To adjust for multiplicity, a two stage gate-keeping test strategy was applied. As the first stage of the procedure, sTST and log_sTSO were compared between gaboxadol 15 mg and placebo during week 1 using Hochberg's procedure [22] (Fig. 1). If at least one of these comparisons was found to be positive, the procedure would continue to stage 2 where gaboxadol 15 mg was compared to placebo at week 2 for sTST, log_sTSO, sNAW and sQUAL, again using Hochberg's procedure. Doses were tested in a hierarchical fashion. That is, gaboxadol 15 mg was tested, and if positive, then gaboxadol 10 mg was tested, etc. Efficacy variables outside the testing strategy were performed using MMRM, but with no multiplicity adjustment. For these variables, the term "statistical significance" refers to any *p*-value <0.05 but not part of the formal testing strategy.

For the evaluation of rebound insomnia an analysis was performed using a dichotomised "rebound" variable: a patient was categorised as having rebound insomnia if the TST value on the first day of the run-out phase was shorter than the shortest sTST value during the run-in phase. This was repeated for days 2 and 3 of the run-out phase. The treatment groups were compared using Fisher's exact test. The above analyses were repeated using sTSO as the outcome variable. As a *post-hoc* analysis, the changes from baseline in sTST and sTSO at days 1, 2 and 3 were compared between the active treatment groups and placebo (FAS, OC, ANCOVA).

Analyses of routine safety measures were descriptive only, and no formal testing was performed.

Data from the benzodiazepine Withdrawal Symptoms Questionnaire [21] during days 1, 2 and 3 in the run-out phase were analysed using a dichotomised variable: a patient had a withdrawal signal if three or more items were new or had worsened since baseline (day 15). The treatment groups were compared pairwise using χ^2 tests. Each active treatment group was compared with its corresponding placebo group and also, on an exploratory basis, with the overall placebo group.

The principal statistical software used for the data analyses was SAS® version 9.1.

2.7. Statistical power

The primary efficacy objective was to compare the hypnotic efficacy (sTST) of three different dose levels of gaboxadol (5, 10, and 15 mg daily) with placebo in patients with primary insomnia over 2 weeks of treatment. With 734 patients, the study had an overall power of approximately 76% for finding pre-defined true effects on both sTST and sTSO simultaneously, in which case the power is 95% for finding at least one parameter significant. If only one parameter has a true effect, the power for finding this is 80%.

3. Results

3.1. Patient accounting and baseline characteristics

Of the 1298 patients screened, a total of 742 patients were randomized, 741 were treated and 648 (87%) of these completed the 2-week treatment phase and the 1-week run-out phase. See also Supplementary Fig. 1. The most frequent reasons for discontinuation were lack of efficacy in the gaboxadol 5 mg (3%), adverse events and lack of efficacy in the gaboxadol 10 mg group (both 3%), adverse events in the gaboxadol 15 mg (10%) and zolpidem (7%) groups and protocol violations in the placebo group (6%). Based on a study drug record filled out by the patient, more than 95% of patients took treatment according to the study protocol throughout the entire study.

The baseline characteristics of the patients are shown in Table 1. The treatment groups appeared similar with regard to baseline demographics and efficacy scores (Table 1, Supplementary Tables 1 and 2.

Approximately 60% of patients had a concomitant medical condition and there were no major differences between the groups. The most common concomitant conditions were musculoskeletal and connective tissue disorders (15–24%) and vascular disorders (10–16%).

3.2. Efficacy

3.2.1. 2-week treatment phase

The effects of gaboxadol (changes from baseline) on sleep maintenance and onset measures during the 2-week treatment phase are presented in Supplementary Table 1 and Fig. 2 (absolute values). Generally, gaboxadol and the active reference zolpidem improved sleep onset and maintenance. For all hypotheses in the formal statistical testing strategy, a statistically significant improvement compared to placebo was seen for gaboxadol

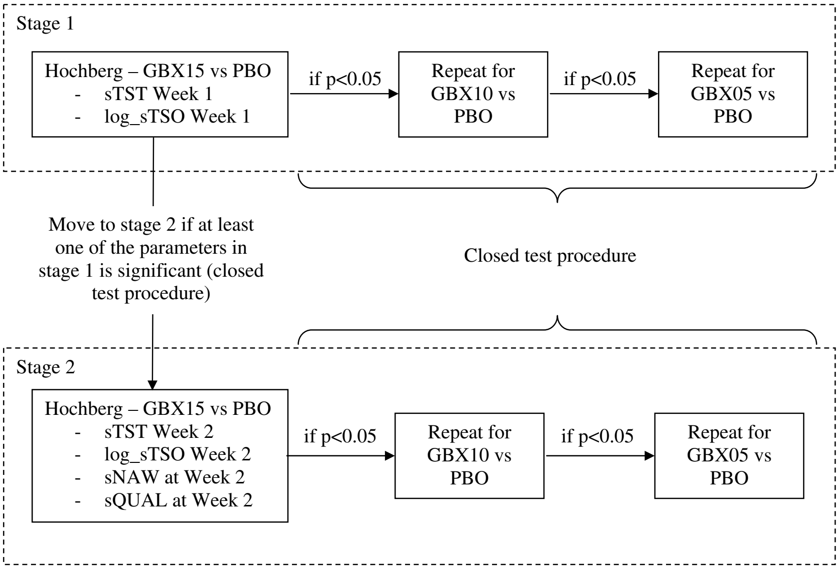

Fig. 1. Formal testing strategy. Stage 1 hypotheses (involving sTST and log_sTSO for GBX15 versus PBO at week 1) were tested at the 0.05 level using Hochberg's procedure. If significant, the lower doses could be tested in a stepwise manner using a closed test procedure. For variables found significant at week 1, a similar step-down procedure could be performed on week 2 data (stage 2). sNAW and sQUAL could be tested at week 2 if at least one of the variables at stage 1 was significant. PBO placebo; GBX05 gaboxadol 5 mg; GBX10 gaboxadol 10 mg; GBX15 gaboxadol 15 mg.

Table 1
Baseline patient characteristics.

		PBO ($N = 142$)	GBX05 ($N = 145$)	GBX10 ($N = 151$)	GBX15 ($N = 153$)	ZOL ($N = 150$)
Characteristic						
Females	%	64.1	60.0	63.6	63.4	66.7
Caucasians	%	99.3	98.6	99.3	99.3	95.3
Age (y)	Mean ± SD	49.7 ± 10.6	48.4 ± 11.0	48.5 ± 11.4	48.3 ± 12.2	45.9 ± 11.1
Body mass index (kg/m^2)	Mean ± SD	25.6 ± 4.7	25.7 ± 5.2	25.1 ± 3.7	25.0 ± 3.8	25.6 ± 4.6

PBO, placebo; GBX05, gaboxadol 5 mg; GBX10, gaboxadol 10 mg; GBX15, gaboxadol 15 mg; ZOL, zolpidem 10 mg.

15 mg at week 1 ($p < 0.001$) and week 2 ($p < 0.05$). In addition, statistically significant improvements were seen for gaboxadol 5 and 10 mg at week 1 ($p < 0.01$), for gaboxadol 10 mg on sTST, sNAW and SQUAL at week 2 ($p < 0.05$) and for gaboxadol 5 mg on sTST at week 2 ($p < 0.05$). Numerically, the data suggest that the effects of gaboxadol on sleep maintenance were dose-related, with the 15-mg dose being the most effective of the doses, although this was not formally tested.

As for sTST, the improvements observed on sNAW and sWASO seemed to be dose-related, although the effect levels were slightly lower and did not reach statistical significance for the lower dose(s) of gaboxadol. It should be noted, however, that the sample size for sWASO was approximately 60% of the total sample size since the question addressing this parameter was introduced in the e-diaries after study start.

With regard to sleep onset, at week 1 all gaboxadol doses and zolpidem significantly improved sTSO. There was no obvious dose effect for gaboxadol.

Results for the self-reported sleep quality (sQUAL) and freshness after sleep (sFRESH) and Leeds Sleep Evaluation Questionnaire (LSEQ) are shown in Supplementary Table 2. sQUAL and sFRESH significantly improved for all doses of gaboxadol and for zolpidem at both weeks ($p < 0.01$) (except gaboxadol 5 mg at week 2). The results from the LSEQ generally supported the results obtained with the sleep diary.

The effects of treatment on patients' ratings of daytime function and energy are shown in Fig. 3. Gaboxadol 10 and 15 mg significantly improved daytime function and energy at both weeks ($p < 0.05$), whereas gaboxadol 5 mg only improved daytime function at week 2 ($p < 0.05$). Zolpidem also showed benefits on these measures ($p < 0.001$).

When statistical analyses for sTST and sTSO were repeated on the per-protocol set (a subset of the full analysis set, excluding major protocol violators) results leading to the same conclusions as described above were obtained. Also, analyses based on the worst observation carried forward (WOCF) and a non-parametric ranking

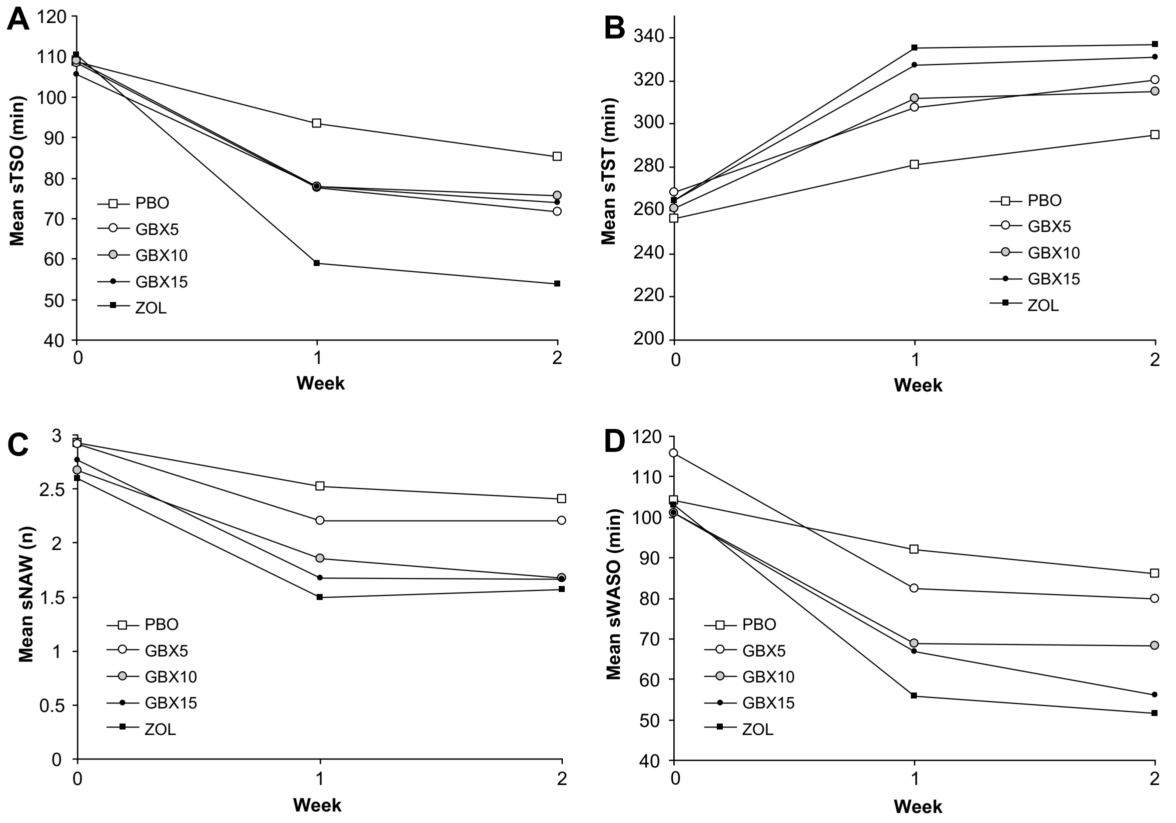

Fig. 2. Patient-rated assessment of sleep maintenance and onset during the 2-week, double-blind treatment phase. PBO placebo; GBX05 gaboxadol 5 mg; GBX10 gaboxadol 10 mg; GBX15 gaboxadol 15 mg; ZOL zolpidem 10 mg; sTST self-reported total sleep time (A); sTSO self-reported time-to-sleep onset (B); sNAW self-reported number of nocturnal awakenings (C); sWASO self-reported wakefulness after sleep onset (D). (Sample sizes were smaller for this measure because the variable was added after the study had started).

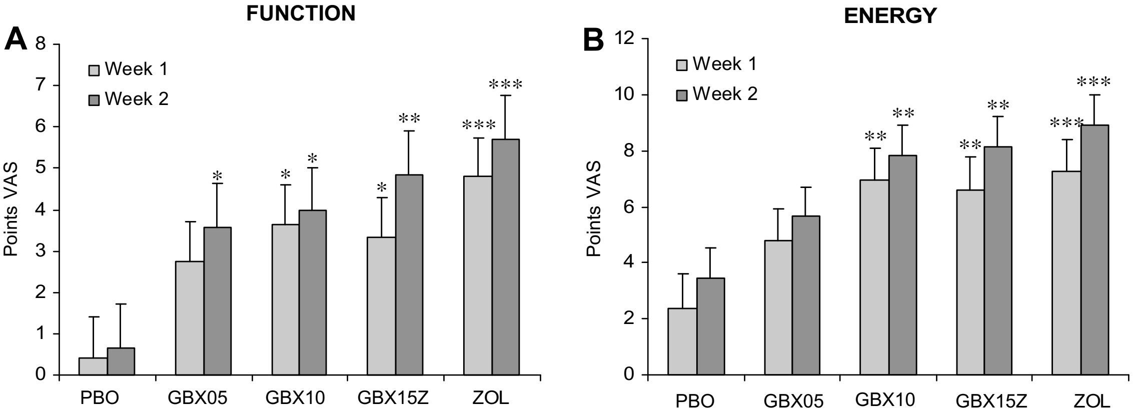

Fig. 3. Mean changes from baseline (±SE) for daytime function (A) and energy (B) during the 2-week, double-blind treatment phase. GBX05 gaboxadol 5 mg; GBX10 gaboxadol 10 mg; GBX15 aboxadol 15 mg; ZOL zolpidem 10 mg; $^{*}p \leqslant 0.05$, $^{**}p \leqslant 0.01$, $^{***}p \leqslant 0.001$ versus placebo. For both measures, a higher score indicates greater improvement relative to placebo.

test, taking time to discontinuation and reason for discontinuation into account, confirmed the results obtained with parametric test methods. Covariate analyses showed no statistically significant interaction between sex and treatment ($p = 0.47$) at week 1, although subgroup analyses indicated a trend towards greater efficacy of gaboxadol on sTST in women than in men.

3.2.2. Randomised run-out phase

The analysis of rebound insomnia, defined as the proportion of patients with a lower sTST value after the first night of the run-out phase compared to the lowest sTST value during the run-in phase, is shown in Table 2a. The statistical analysis was based on the group of patients that were switched from active treatment to placebo during the run-out phase compared to the overall placebo group. The proportion of patients with a rebound signal was not significantly different from the proportion in the overall placebo group ($p > 0.17$ for all gaboxadol groups) for any of the gaboxadol doses. For zolpidem 10 mg, a transient rebound insomnia was observed on day 1 ($p < 0.01$).

Evaluation of rebound insomnia based on sTSO led to the same conclusions as sTST (Table 2b). There was a transient rebound insomnia for zolpidem on day 1 ($p < 0.05$).

Post-hoc analyses showed that the mean sTST value on day 1 was above the baseline values for gaboxadol 5 and 10 mg, and no statistically significant difference to placebo was seen (data not shown). For gaboxadol 15 mg and zolpidem, the mean sTST value on day 1 was 18–19 min below the baseline value and the difference to placebo (44–45 min) was statistically significant ($p < 0.01$). On days 2 and 3, sTST values were above baseline level and not significantly different from placebo. For sTSO, a significant difference to placebo was only seen for zolpidem on day 1 (37 min, $p < 0.001$, data not shown).

3.3. Safety

During the 2-week double-blind treatment phase, approximately 50% of all patients had one or more adverse events (Table 3). Headache, dizziness, and nausea were the most frequent adverse events. Most of the cases lasted less than 2 days and were mostly mild to moderate. In the placebo, gaboxadol 10 mg, and gaboxadol 15 mg groups the incidences of adverse events were approximately 10% points higher in women than in men. The sex difference was most pronounced for dizziness, nausea and vomiting.

During the 2-week treatment phase, five patients had a serious adverse event (SAE), of which four were considered related to treatment [radius fracture due to fall on an icy, slippery street on day 3 (gaboxadol 15 mg), syncope (2 days after last intake of gaboxadol 10 mg), depression lasting 5 days (zolpidem), and agitation lasting 1 day (zolpidem)]. One SAE was considered not related to treatment (gaboxadol 15 mg); a 47-year-old woman became pregnant during the 2-week treatment phase and had an abortion due to fetal death after the study.

During the run-out phase (week 3) approximately 25% of the patients had adverse events. The incidence of adverse events in the run-out phase was similar in all treatment groups. Discontinuation of active treatment did not appear to induce additional adverse events (data not shown). Two patients withdrew due to

Table 2
Proportion of patients (%) with rebound signal based on sTST (A) or sTSO (B) in the randomised run-out phase.

A	PBO (PBO) $N = 126$	GBX05 (PBO) $N = 59$	GBX10 (PBO) $N = 65$	GBX15 (PBO) $N = 64$	ZOL (PBO) $N = 67$
Day 1	6.3	10.2	6.2	12.5	19.4[**]
Day 2	5.5	6.9	4.6	7.8	7.6
Day 3	3.9	6.9	1.5	3.1	7.5
B	PBO (PBO) $N = 126$	GBX05 (PBO) $N = 59$	GBX10 (PBO) $N = 63$	GBX15 (PBO) $N = 63$	ZOL (PBO) $N = 67$
Day 1	6.3	3.4	7.9	12.7	17.9[*]
Day 2	3.2	5.2	6.2	9.5	6.1
Day 3	3.9	1.7	10.8	3.1	7.5

PBO, placebo; GBX05, gaboxadol 5 mg; GBX10, gaboxadol 10 mg; GBX15, gaboxadol 15 mg; ZOL, zolpidem 10 mg. The treatment before the brackets is the treatment assigned during the 2-week treatment phase, the treatment inside the brackets is the treatment assigned during the 1-week randomised run-out phase. A patient had a rebound signal if theTST/sTSO value on the particular day of the randomised run-out phase was worse than the worst sTST/sTSO value during the run-in phase.

[*] $p \leqslant 0.05$.

[**] $p \leqslant 0.01$ versus placebo.

Table 3
Summary of clinical adverse events during the 2-week, double-blind, treatment phase.

	PBO ($N = 142$)		GBX05 ($N = 145$)		GBX10 ($N = 151$)		GBX15 ($N = 153$)		ZOL ($N = 150$)	
Patients with	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
⩾1 AE	57	(40.1)	66	(45.5)	66	(43.7)	90	(58.8)	84	(56.0)
⩾1 serious AE	0	(0.0)	0	(0.0)	1	(0.7)	2	(1.3)	2	(1.3)
⩾1 AE leading to discontinuation	4	(2.8)	1	(0.7)	4	(2.6)	14	(9.2)	10	(6.7)
Specific AEs with incidence ⩾5%										
Headache	17	(12.0)	14	(9.7)	16	(10.6)	29	(19.0)	29	(19.3)
Dizziness	4	(2.8)	8	(5.5)	13	(8.6)	24	(15.7)	14	(9.3)
Nausea	2	(1.4)	6	(4.1)	7	(4.6)	14	(9.2)	7	(4.7)
Somnolence	4	(2.8)	4	(2.8)	4	(2.6)	8	(5.2)	3	(2.0)
Vomiting	0	(0.0)	1	(0.7)	1	(0.7)	8	(5.2)	3	(2.0)

PBO, placebo; GBX05, gaboxadol 5 mg; GBX10, gaboxadol 10 mg; GBX15, gaboxadol 15 mg; ZOL, zolpidem 10 mg; AE, adverse event.

adverse events. The analyses of the Withdrawal Symptoms Questionnaire (based on either the total number of withdrawal symptoms versus baseline, or a dichotomised variable of whether 3 or more items worsened for a patient since baseline) did not reveal withdrawal symptoms in any of the treatment groups (Table 4).

In the safety follow-up phase, one patient had an SAE (high hepatic enzyme value) considered not related to treatment (gaboxadol 15 mg).

No deaths occurred over the course of the entire study. There were no clinically relevant changes within or differences between treatment groups in laboratory values, vital signs, weight changes or ECGs.

4. Discussion

The efficacy analyses showed that gaboxadol improved sleep onset (sTSO) and maintenance (sTST, sNAW and sWASO). For the sleep maintenance parameters, the effects appeared to be dose-related, with the 15-mg dose tending to be the most effective dose studied.

The significant effect of zolpidem on sleep onset and maintenance parameters relative to placebo at weeks 1 and 2 validates the design and study conduct. At week 1, the magnitude of effect on the sleep maintenance parameter sTST was numerically similar and in the range of 20–40 min for both gaboxadol 15 mg and zolpidem. A numerically smaller magnitude of effect on sleep onset (sTSO) was observed for all gaboxadol doses compared to zolpidem.

The elimination half-life of gaboxadol (approximately 1.5 h) [23] is slightly shorter than that of zolpidem (approximately 2.5 h) [24], and yet there appears to be a beneficial effect of gaboxadol on the sleep maintenance measures of wakefulness. Traditionally, the prediction of sleep maintenance efficacy for benzodiazepine-site ligands, such as zolpidem, has focused on the pharmacokinetics of the drug. The described effect of gaboxadol on the sleep maintenance parameters of wakefulness indicates that the mechanism of action may also be important for the achieved hypnotic effects.

The observed improvements on sleep onset and maintenance support findings on both objective (PSG) and subjective measures (self-reported) in previous clinical studies of gaboxadol in healthy subjects in models of transient insomnia [10,11] as well as in primary insomnia patients [12,13]. In two early-phase exploratory studies in primary insomnia patients ($N = 23$ and 38)[12,13] using PSG, short-term treatment with gaboxadol (15 and 20 mg, respectively) improved total sleep time, wakefulness after sleep onset, number of awakenings (20 mg only) and sleep onset (15 mg only). In addition, improvements in various parameters assessing sleep quality were observed [11–13].

In the gaboxadol and zolpidem groups of the current study, the effects on sleep were associated with an improved perceived sleep quality (sQUAL), freshness after sleep (sFRESH) and daytime function. In previous PSG studies, gaboxadol has demonstrated consistent increases in SWS and enhancement of power density in the SWA and theta frequency bands without suppression of REM sleep [10–13,25–28]. This unique profile of gaboxadol with respect to sleep architecture, however, does not seem to distinguish gaboxadol from zolpidem in terms of subjective measures of sleep quality and associated daytime function. One may speculate that more sensitive objective and subjective measures for sleep quality and daytime function may reveal a difference between zolpidem and gaboxadol in future studies. In fact, Walsh et al. [29] have reported positive effects of increased slow wave sleep following gaboxadol on daytime sleepiness using multiple sleep latency test as an objective assessment. A recent NIH conference identified the use of objective assessment of functional outcomes as a prioritised area for future research within insomnia treatment development [30].

In addition to the VAS scale based measure, sQUAL, sleep quality was assessed in the LSEQ. Results from the latter were well in

Table 4
Proportion of patients (%) with withdrawal signals in the randomised run-out phase, using day 15 as baseline.

Run-out day	Proportion of patients with withdrawal signals (defined as ⩾3 new or worsened withdrawal symptoms)								
	PBO (PBO) (%)	GBX05 (PBO) (%)	GBX05 (GBX05) (%)	GBX10 (PBO) (%)	GBX10 (GBX10) (%)	GBX15 (PBO) (%)	GBX15 (GBX15) (%)	ZOL (PBO) (%)	ZOL (ZOL) (%)
1	11.4	11.3	12.3	6.3	4.8	11.9	5.3	5.0	7.0
2	12.8	11.3	4.6	3.3[a,b]	11.1	10.0	5.4	1.7[*,b]	10.5
3	14.5	11.1	12.5	8.1	6.3	10.2	7.1	8.6	7.0
1–3	29.9	24.1	21.5	17.5[a,b]	15.9	23.3	22.8	16.7[a,b]	24.6

PBO, placebo; GBX05, gaboxadol 5 mg; GBX10, gaboxadol 10 mg; GBX15, gaboxadol 15 mg; ZOL, zolpidem 10 mg. The treatment before the brackets is the treatment assigned during the 2-week treatment phase, the treatment inside the brackets is the treatment assigned during the 1-week randomised run-out phase. A patient had a rebound signal if he/she had three or more new or worsened withdrawal symptoms according to the Benzodiazepine Withdrawal Symptom Questionnaire.

[*] $p < 0.05$ versus the PBO (PBO) group.

[a] $p < 0.08$ versus the PBO (PBO) group, borderline statistical significance.

[b] Note that this group had a lower proportion of patients with a withdrawal signal than in the PBO (PBO) group (overall placebo group).

line with sQUAL results, which further strengthen the observations on the VAS scale based measure.

Also, the present study is one of the first studies to include a 1-week randomised, double-blind run-out phase to assess rebound insomnia and withdrawal effects. With the *a priori* definition of rebound insomnia (based on sTST and sTSO), no rebound effect was observed for any of the gaboxadol treatment groups. Transient rebound insomnia on day 1 was found for zolpidem, based on sTST and sTSO. Further analyses (*post-hoc*) showed transient rebound insomnia on day 1 of the run-out phase for gaboxadol 15 mg based on sTST but not sTSO. As for the *a priori* analysis, transient rebound insomnia on day 1 was found for zolpidem, based on both sTST and sTSO. Evaluation of rebound insomnia following long-term treatment should be performed to confirm the lack of rebound effect after discontinuation of gaboxadol treatment.

Gaboxadol was generally safe and well tolerated in this adult population with primary insomnia. The overall discontinuation rate was 13% which was comparable to that in other outpatient studies in insomnia [15,31,32]. The discontinuation rates were highest in the placebo and gaboxadol 15 mg groups, but only a small percentage of patients discontinued due to adverse events. The most common adverse events leading to discontinuation were headache and dizziness in the gaboxadol 15 mg group and depression in the zolpidem group. During the 2-week treatment phase, common adverse events associated with gaboxadol were dizziness, nausea and somnolence, in agreement with previous publications [33–37].

In conclusion, this study showed that gaboxadol 15 mg treatment for 2 weeks significantly improved all sleep onset and maintenance parameters as well as sleep quality and daytime function, as did zolpidem 10 mg. Gaboxadol 5 and 10 mg also showed beneficial effects on most efficacy parameters, although the effect was not sustained to the same extent during week 2. Gaboxadol was generally safe and well tolerated, with no evidence of withdrawal symptoms or rebound insomnia after discontinuation of short-term treatment. For zolpidem 10 mg, transient rebound insomnia was observed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.sleep.2008.09.010.

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